CLAIMS

What is claimed is:

1. A crystalline polypeptide, said polypeptide comprising the catalytic domain of a Tie-2 protein.

2. The crystalline polypeptide of Claim 1 wherein the polypeptide comprises the catalytic domain of human Tie-2.

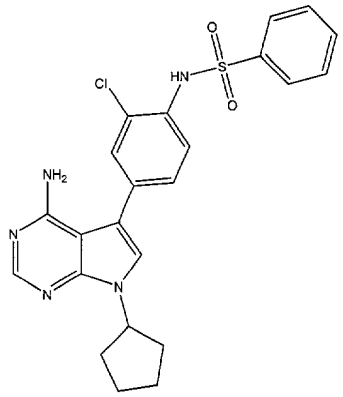
3. A crystalline polypeptide-ligand complex, said polypeptide comprising the catalytic domain of a Tie-2 protein.

4. The crystalline polypeptide/ligand complex of Claim 3 wherein the polypeptide comprises the catalytic domain of a mammalian Tie-2.

5. The crystalline polypeptide/ligand complex of Claim 4 wherein the mammalian Tie-2 protein is human Tie-2.

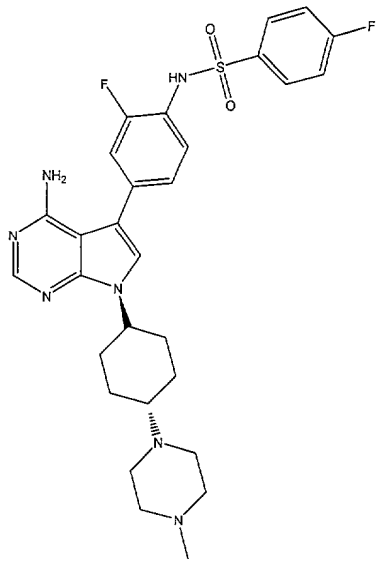
6. The crystalline polypeptide/ligand complex of Claim 5 wherein the polypeptide comprises amino acids 802-1124 of SEQ ID NO: 1.

7. The crystalline polypeptide/ligand complex of Claim 6 wherein the ligand is of the formula:



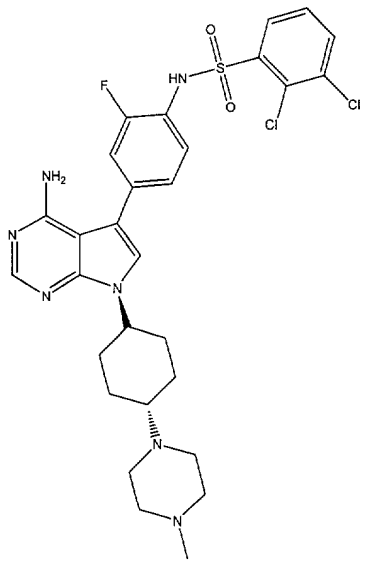
8. The crystalline polypeptide/ligand complex of Claim 7 having unit cell parameters a is about 96 Å, b is about 118 Å, c is about 78 Å and $\alpha = \beta = \gamma = 90^{\circ}$.

9. The crystalline polypeptide/ligand complex of Claim 6 wherein the ligand is of the formula:



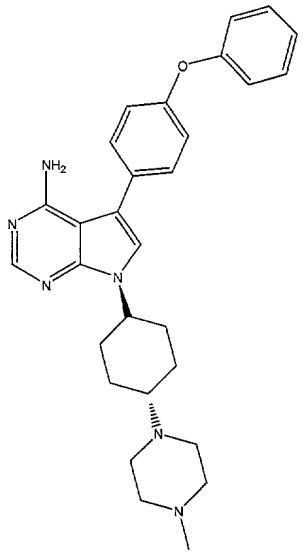
10. The crystalline polypeptide/ligand complex of Claim 9 having unit cell parameters a and b are about 86.0 Å, c is about 112.0 Å and $\alpha = \beta = \gamma = 90^{\circ}$.

11. The crystalline polypeptide/ligand complex of Claim 6 wherein the ligand is of the formula:



12. The crystalline polypeptide/ligand complex of Claim 11 having unit cell parameters a and b are about 86.0 Å, and c is about 112.0 Å and $\alpha = \beta = \gamma = 90^{\circ}$.

13. The crystalline polypeptide/ligand complex of Claim 6 wherein the ligand is of the formula:



14. The crystalline polypeptide/ligand complex of Claim 13 having unit cell parameters a and b are about 86.0 Å, c is about 112.0 Å and $\alpha = \beta = \gamma = 90^{o}$.

15. A method of determining the three dimensional structure of a first polypeptide comprising the catalytic domain of a Tie-2 protein, said method comprising the steps of:

(a) obtaining a crystal of the first polypeptide comprising the catalytic domain of Tie-2;

(b) obtaining x-ray diffraction data for said crystal; and

(c) solving the crystal structure of said crystal using the atomic coordinates of a second polypeptide and said x-ray diffraction data, said second polypeptide comprising the catalytic domain of a Tie-2 protein.

16. The method of Claim 15 wherein the crystal of the first polypeptide comprises the first polypeptide complexed with a ligand.

17. The method of Claim 15 wherein the first polypeptide comprises the catalytic domain of a mammalian Tie-2 protein.

18. The method of Claim 17 wherein the first polypeptide and the second polypeptide, independently, comprise the catalytic domain of a human Tie-2 protein.

19. The method of Claim 18, wherein the first polypeptide comprises the catalytic domain of wild type human Tie-2 and the second polypeptide comprises the catalytic domain of wild type human Tie-2.

20. The method of Claim 19, wherein the first polypeptide comprises the catalytic domain of wild type human Tie-2.

21. A method of identifying a compound which is an inhibitor of a Tie-2 protein, said method comprising the steps of

(a) obtaining the atomic coordinates of a crystal of a polypeptide comprising the catalytic domain of a Tie-2 protein;

(b) using said atomic coordinates to define the active subsites of Tie-2; and

(c) identifying a compound which binds to the one or more active subsite; wherein the compound which bind to the active subsite or sites is an inhibitor of a Tie-2 protein.

22. The method of Claim 21, further comprising the step of

(d) assessing the ability of the compound identified in step (c) to inhibit Tie-2.

23. The method of Claim 21 wherein the Tie-2 protein is a mammalian protein.

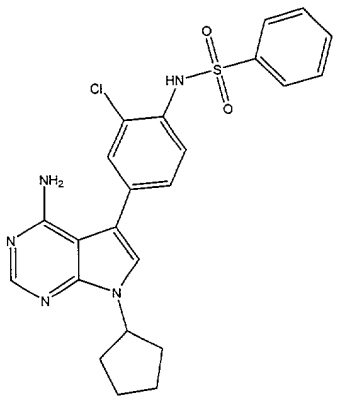
24. The method of Claim 22 wherein the Tie-2 protein is a human protein.

25. The method of Claim 24, wherein the Tie-2 protein is wild type human Tie-2.

26. The method of Claim 21 wherein said crystal further comprises a ligand bound to said catalytic domain.

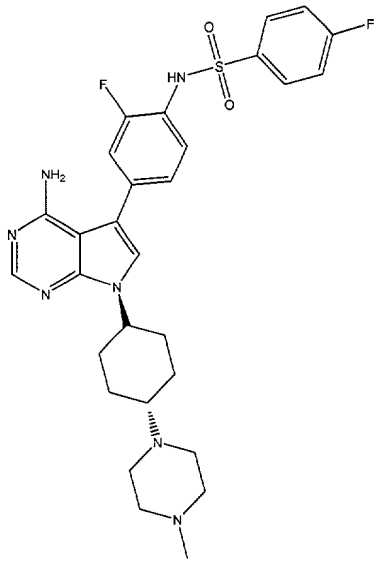
27. The method of Claim 24 wherein the polypeptide comprises amino acids 802-1124 of SEQ ID NO: 1.

28. The method of Claim 24, wherein the ligand is of the formula:



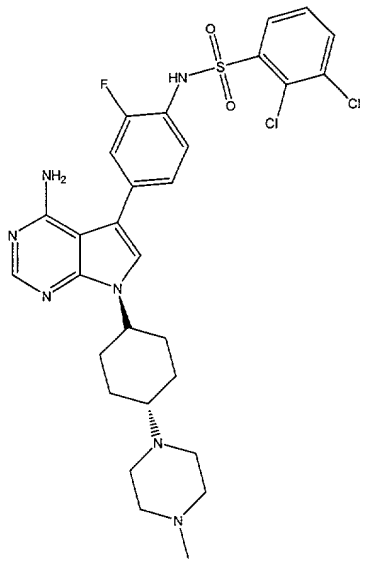
29. The method of Claim 28, wherein the crystal has unit cell parameters wherein a is about 96 Å, b is about 118 Å, c is about 78 Å and $\alpha = \beta = \gamma = 90^{\circ}$.

30. The method of Claim 24,wherein the ligand is of the formula:



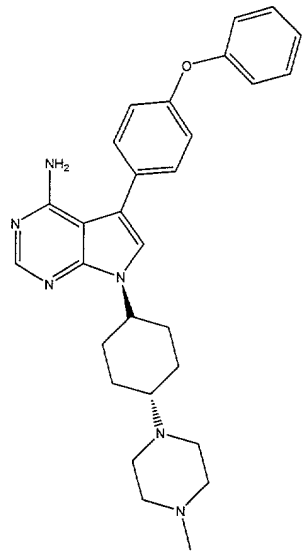
31. The method of Claim 30, wherein the crystal has unit cell parameters wherein a and b are about 86.0 Å, c is about 112.0 Å and $\alpha = \beta = \gamma = 90^{o}$.

32. The method of Claim 24, wherein the ligand is of the formula:



33. The method of Claim 32, wherein the crystal has unit cell parameters wherein a and b are about 86.0 Å, and c is about 112.0 Å and $\alpha = \beta = \gamma = 90^{o}$.

34. The method of Claim 24, wherein the ligand is of the formula:



35. The method of Claim 34, wherein the crystal has unit cell parameters wherein a and b are about 86.0 Å, c is about 112.0 Å and $\alpha = \beta = \gamma = 90^{\circ}$.

36. A method of identifying a compound which is a potential inhibitor of a Tie-2 protein, said method comprising the step of designing a compound that will interact with one or more subsites in the catalytic domain of the Tie-2 protein, based upon the crystal structure coordinates of a polypeptide comprising the catalytic domain; wherein said compound is identified as a potential inhibitor of the Tie-2 protein.

37. The method of Claim 36 wherein the Tie-2 protein is a mammalian Tie-2 protein.

38. The method of Claim 37 wherein the Tie-2 protein is a human Tie-2 protein.

39. The method of Claim 38, wherein the Tie-2 protein is wild type human Tie-2.

40. The method of Claim 39 wherein the polypeptide comprises amino acids 802-1124 of SEQ ID NO: 1.

41. The method of Claim 38 wherein the crystal structure coordinates are set forth in Fig. 3.

42. The method of Claim 38 wherein the crystal structure coordinates are set forth in Fig. 4.

43. The method of Claim 38 wherein the crystal structure coordinates are set forth in Fig. 5.

44. The method of Claim 38 wherein the crystal structure coordinates are set forth in Fig. 6.

45. The method of Claim 38 wherein the compound interacts with one or more of subsites 1 to 9.

46. The method of Claim 45 wherein the compound interacts with two or more of subsites 1 to 9.

47. The method of Claim 46 wherein the compound interacts with three or more of subsites 1 to 9.

48. The method of Claim 46 wherein the compound interacts with a set of subsites comprising subsite 1 and subsite 2.

49. The method of Claim 47 wherein the compound interacts with a set of subsites

comprising subsite 1, subsite 2 and subsite 3.

50. The method of Claim 47 wherein the compound interacts with a set of subsites comprising subsite 1, subsite 2 and subsite 8.

51. The method of Claim 47 wherein the compound interacts with a set of subsites comprising subsite 1, subsite 2, subsite 3 and subsite 8.

52. The method of Claim 47 wherein the compound interacts with a set of subsites comprising subsite 1, subsite 4 and subsite 5.

53. The method of Claim 47 wherein the compound interacts with a set of subsites comprising subsite 1, subsite 2, subsite 7 and subsite 8.

54. The method of Claim 47 wherein the compound interacts with a set of subsites comprising subsite 1, subsite 2, subsite 3, subsite 7 and subsite 8.

55. The method of Claim 47 wherein the compound interacts with a set of subsites comprising subsite 1, subsite 2, subsite 3, subsite 7 and subsite 8.

56. The method of Claim 47 wherein the compound interacts with a set of subsites comprising subsite 1, subsite 2, subsite 4, subsite 6 and subsite 8.

57. The method of Claim 47 wherein the compound interacts with a set of subsites comprising subsite 1, subsite 2, subsite 3, subsite 4, subsite 6 and subsite 8.

58. The method of Claim 47 wherein the compound interacts with a set of subsites comprising subsite 1, subsite 2, subsite 3, subsite 4, subsite 6 and subsite 8.

59. A Tie-2 inhibitor comprising two or more of the following:

(a) a hydrogen bond donor positioned to interact with Glu 903 of human Tie-2;

(b) a hydrogen bond acceptor positioned to interact with Ala 905 of human Tie-2;

(c) a hydrogen bond donor positioned to interact with Ala 905 of human Tie-2;

(d) a hydrophobic moiety positioned to interact with one or more of Ile 830, Val 838, Ala 853, Ile 886, Ile 902, Tyr 904, Ala 905 and Leu 971 of human Tie-2;

(e) a hydrogen bond donor or positively charged functional group positioned to interact with Asp 912 of human Tie-2;

(f) a hydrogen bond donor or hydrogen bond acceptor postioned to interact with Asn 909 of human Tie-2;

(g) a hydrophobic moiety positioned to interact with one or more of Val 838, Lys 855, Ile 886, Ile 902, Leu 971 and Ala 981 of human Tie-2;

(h) a hydrogen bond acceptor or negatively charged functional group positioned to interact with Lys 855 of human Tie-2;

(i) a hydrogen bond acceptor positioned to interact with Asp 982 of human Tie-2;

(j) a hydrogen bond acceptor positioned to interact with Phe 983 of human Tie-2;

(k) a hydrophobic moiety positioned to interact with one or more of Leu 873, Leu 876, Ile 885, Ile 886, Leu 888, Leu 900, Ile 902, Ala 981 and Phe 983 of human Tie-2;

(l) a hydrogen bond donor or positively charged functional group positioned to interact with Asp 982 of human Tie-2;

(m) a hydrogen bond donor positioned to interact with Ile 886 of human Tie-2;

(n) a hydrogen bond donor positioned to interact with Leu 768 of human Tie-

2;

(o) a hydrogen bond acceptor positioned to interact with Gly 831 of human Tie-2;

(p) a hydrogen bond donor or positively charged functional group positioned to interact with Glu 832 of human Tie-2;

(q) a hydrogen bond acceptor or negatively charged functional group positioned to interact with Lys 840 of human Tie-2;

(r) a hydrogen bond acceptor or negatively charged functional group positioned to interact with Lys 916 of human Tie-2;

(s) a hydrogen bond acceptor or negatively charged functional group positioned to interact with Arg 968 of human Tie-2;

(t) a hydrogen bond donor positioned to interact with Arg 968 of human Tie-2.

60. The Tie-2 inhibitor of Claim 59 comprising (b) and (d).

61. The Tie-2 inhibitor of Claim 59 comprising (d) and at least one of (a), (b) and (c).

62. The Tie-2 inhibitor of Claim 59 comprising (d) and at least two of (a), (b) and (c).

63. The Tie-2 inhibitor of Claim 62 further comprising at least one of (e) and (f).

64. The Tie-2 inhibitor of Claim 62 further comprising (g).

65. The Tie-2 inhibitor of Claim 63 further comprising (g).

66. The Tie-2 inhibitor of Claim 64 further comprising (k).

67. The Tie-2 inhibitor of Claim 65 further comprising (k).

68. The Tie-2 inhibitor of Claim 62 further comprising at least one of (i) and (j).

69. The Tie-2 inhibitor of Claim 63 further comprising at least one of (i) and (j).

70. The Tie-2 inhibitor of Claim 66 further comprising at least one of (i) and (j).

71. The Tie-2 inhibitor of Claim 67 further comprising at least one of (i) and (j).

72. The Tie-2 inhibitor of Claim 59, wherein the inhibitor has a Ki of at least about 1 mM.

73. The Tie-2 inhibitor of Claim 59, wherein the inhibitor has a Ki of at least about 100 μM.

74. The Tie-2 inhibitor of Claim 59, wherein the inhibitor has a Ki of at least about 10 μM.

75. The Tie-2 inhibitor of Claim 59, wherein the inhibitor selectively binds Tie-2 receptors.

76. A method of treating a Tie-2 dependent condition in a patient comprising the step of administering to the patient a therapeutically effective amount of a Tie-2 inhibitor of Claim 59.

77. The method of Claim 76 wherein the patient is a human.

78. The method of Claim 76 wherein the Tie-2 dependent condition is characterized by excessive vascular proliferation.

79. The method of Claim 78 wherein the Tie-2 dependent condition is a hyperproliferative disorder, cancer, a cardiovascular condition, an ocular condition, von Hippel Lindau disease, pemphigoid, psoriasis, Paget's disease, polycystic kidney disease, fibrosis, sarcoidosis, cirrhosis, thyroiditis, Osler-Weber-Rendu disease, chronic inflammation, synovitis, inflammatory bowel disease, Crohn's disease, rheumatoid arthritis, osteoarthritis, psoriatic arthritis, an ulcer or sepsis.

80. The method of Claim 79, wherein the condition is a cancer selected from the group consisting of solid tumor, a sarcoma, fibrosarcoma, osteoma, melanoma, retinoblastoma, a rhabdomyosarcoma, glioblastoma, neuroblastoma, teratocarcinoma, an hematopoietic malignancy, malignant ascites, Kaposi's sarcoma, Hodgkin's disease, lymphoma, myeloma and leukemia.

81. The method of Claim 79 wherein the condition is a cardiovascular condition selected from the group consisting of atherosclerosis, restenosis, ischemia/reperfusion injury, chronic occlusive pulmonary disease, vascular occlusion, carotid obstructive disease, Crow-Fukase (POEMS) syndrome, anemia, ischemia, infarct, and vascular leakage disorders.

82. The method of Claim 79 wherein the condition is an ocular condition selected from the group consisting of ocular or macular edema, ocular neovascular disease, scleritis, radial keratotomy, uveitis, vitritis, myopia, optic pits, chronic retinal detachment, post-laser treatment complications, conjunctivitis, Stargardt's disease, Eales disease, retinopathy, macular degeneration and microangiopathy.

83. The method of Claim 76, wherein the disorder involves aberrant endothelial-periendothelial interactions.

84. A method of decreasing fertility in a patient comprising the step of administering to the patient a therapeutically effective amount of a Tie-2 inhibitor of Claim 59.

85. A method of promoting angiogenesis or vasculogenesis in a patient comprising the step of administering to the patient a therapeutically effective amount of a Tie-2 inhibitor of Claim 59.

86. The method of Claim 85, wherein the Tie-2 inhibitor is administered in combination with a pro-angiogenic growth factor.

87. A method of determining the three dimensional structure of a polypeptide comprising the catalytic domain of a Tie-2 protein, said method comprising the steps of:

(a) obtaining a crystal of the polypeptide comprising the catalytic domain of Tie-2;

(b) obtaining x-ray diffraction data for said crystal; and

(c) solving the crystal structure of said crystal.

88. A crystalline polypeptide, said polypeptide comprising a sequence having 80% homology with the catalytic domain of a Tie-2 protein.